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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,968	GERMINO ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/19/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,16-37,39-61 and 72-75* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 8/19/2005 have been entered.

This action is written in response to applicant's correspondence submitted 8/19/2005. Claims 1, 25, 26, 44, 45, and 60 have been amended, claims 5, 12-15, 38, 43 and 62-71 have been canceled, and no claims have been added. Claims 1-4,6-11,16,17,19-29,31-37,39-57,59-61, and 72-75 are pending while claims 18, 30, and 58 have been withdrawn. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Elected embodiments of claims 72-75 are examined herein. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Restriction/Election

Claims 1-4,6-11,16,17,19-29,31-37,39-57, and 59-61, directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: While it was suggested in the applicant-initiated interview of 10/22/2004, that applicant include their 8 primers as a set for further prosecution, better anchoring their claims, it was not suggested that

the original restriction requirement and requirement for sequence election be waived and that applicant consider pending every one of their SNPs and primer pairs individually(e.g. claim 20). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

It should also be noted that Applicant has yet to specify these 8 particular SEQ ID NOS: that correspond to their elected primers. In their original election dated 10/24/2003 applicant's elected the particular primers pairs of SEQ ID NOS: 3 and 4 and the corresponding nested primer pair of SEQ ID NOS: 19 and 20. Since then, through the office actions and an interview with the examiners on 10/22/2004, applicant was apprised that they could prosecute 8 primers(8 SEQ ID NOS), which is to say 2 more pairs than originally elected. However, applicant has yet to include these specific SEQ ID NOS: in their claims and has only prosecuted broad ranges of SEQ ID NO:1. Which is to say, if SEQ ID NO:1 encompasses these 8 sequences, the 8 individual sequences should separately be named, each with their own SEQ ID NO:, not referenced as a part of SEQ ID NO:1. It should be further noted that without any of the previous elections made in the prosecution of this case being prosecuted, it would appear that applicant is pursuing a withdrawn embodiment of their invention. Applicant must clarify which 2 other primer pairs in addition to their already elected SEQ ID NOS: 3, 4, 19, and 20 they intend to prosecute if they should choose to elect as suggested in the interview. Accordingly, claims drawn to any sequence other than to the specific SEQ ID NOS: that make up the elected set of primers, are withdrawn from consideration as being directed to a non-elected invention. As a result the only presently pending claims that are limited to the elected embodiment of 10/24/2003 are claims 72-75 and as such are examined herein. If SEQ ID NO:1 encompasses these 8

sequences, the 8 individual sequences should separately be named, each with their own SEQ ID NO:, not referenced as a part of SEQ ID NO:1. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicant is reminded that from the FAOM(1/29/2004) in response to applicant's initial election;

"The SEQ ID NOS: that were not elected, and claims directed to non-elected subject matter will not be examined as they are considered to be withdrawn until the time of allowance when rejoinder is possible, if warranted. Specifically, claims 18, 30, 58 and 67 are drawn to non-elected subject matter and are considered to be withdrawn. The traversal is on the ground(s) that the examiner's analysis has become tautological. Furthermore the applicant asserts that the different SEQ ID NOS; of their claims could be searched without a burden to the examiner. While the examiner acknowledges the applicants arguments, they are reminded that each of their claimed SEQ ID NOS: is patentably distinct in its structure and in its function. Additionally, a search of each and every SEQ ID NO: within the claims would in fact represent a burden on the office as the applicant has been afforded the opportunity "to include up to 10 nucleotide sequences per application" as instructed by the *Official Gazette* and notices posted on the PTO website.

The examiner retains his/her discretion in the inclusion of "up to 10 sequences." It is further maintained that the examiner adhered to the PTO policy concerning restriction practice as defined in *35 U.S.C. 121*, "if two or more independent and distinct inventions are claimed in one application, the commissioner may require the application to be restricted to one of the inventions." The examiner maintains that the inventions are distinct, each from the other because of the following reasons:

These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Each primer sequence and nucleotide residue are patentably distinct because they are unrelated sequences, i.e. these sequences are unrelated because each has a different nucleotide composition and as a result different physical and biochemical properties and differs in structure and in function and in biological activity, while primers do not encode proteins, their ability to hybridize and subsequently prime amplification is a direct effect of their characteristic nucleic acid arrangement. The Examiner reaffirms that the groups are properly separated as their inclusive products are comprised by different nucleic acid sequences and as a result, create distinct groups with variant structural and functional capacities. The examiner maintains the restriction requirement made previously, as each group is correctly separated as unrelated or patentably distinct and as such make the requirement final."

Furthermore, it is not believed that the claims including non-elected subject matter link the entire claim set, as the newly amended claims no longer read upon the elected invention.

Response to Arguments:

Applicant's arguments filed 8/19/2005 have been fully considered but they are not persuasive. Applicant argues only the portion of the examiner's comments regarding claim 20. Applicant asserts that "claim 20 is not being withdrawn because Applicants made no further amendments to claim 20 in the response filed November 23, 2004 to the office action mailed August 23, 2004". However, the point being made by the examiner was that the only part of claim 20 that was elected on 10/24/2003 was the single mutation occurring at position 3666 in Exon 1 and the non-elected subject matter has still not been cancelled. As a result only the claims containing solely the elected embodiments are presently examined. Again it is reiterated that applicant must consider all subject matter not specifically elected in their 10/24/2003 as withdrawn and as a result it has not been examined to date. Applicant is again encouraged to elucidate the specific 4 primer pairs they intend to claim in response to this and all previous requests for the same if they so choose.

Claim Interpretations

It should be noted that the claim language including "selectively hybridize under highly stringent conditions" is interpreted as being able to hybridize under any sort of high stringency conditions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 72 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536).

Klinger et al. teach a primer comprising a 5' region and adjacent 3' region, said region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence and, optionally, to a PKD1 gene homolog sequence, and said 3' region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence, and not to a PKD1 gene homolog sequence, provided the primer does not consist of a sequence as set forth in SEQ ID NO:11, 18, 52, and 60(Abstract, Col. 5 lines 45-67 – Col. 6 1-4 and figure 3B).

Klinger teaches the above primer wherein said 5'region comprises at least about ten contiguous nucleotides, wherein the 3'region comprises at least one 3'terminal nucleotide identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and wherein said 3' terminal nucleotide is different from a nucleotide that is 5' and adjacent to a nucleotide sequence of the PKD1 homolog to which the 5' region of the primer can hybridize wherein the 3' region comprises about 2 to 4 3' terminal nucleotides and a 5' region of about 14 to 18 nucleotides and a 3' region of about 2 to 6 nucleotides in their teaching of the primer in Figure 3B of 5'AGGACCTGTCCAGGCATC 3'.

Klinger teaches in Col. 5, that the "present invention encompasses isolated oligonucleotides corresponding to sequences within the PKD1 gene and PKD1 cDNA, which, alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides; may be single or double stranded, and may be labeled or modified as described below. An example of an oligonucleotide that can be used in this manner is shown in Fig. 3B"(Col. 5). (Note: art has been applied according to the specification's definition of "substantially identical" on page 21, a primer with "at least about 80% identity to one of SEQ ID NOS: 3 to 51 and 61 to 113")

Klinger et al. teach an isolated polynucleotide, comprising a contiguous sequence of at least about ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto, the contiguous nucleotide sequence comprising a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted(Col. 5 lines 45-67 and Col. 6 lines1-17). Furthermore, the reference teaches that "deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products"(Col. 8 lines 36-40).

Klinger et al. teach the above polynucleotides in a vector and furthermore the host cell transformed by this vector. The abstract teaches that "the invention also encompasses vectors comprising these nucleic acids, host cells transformed with the vectors"(+ Col. 6 lines 39-67 and Col. 7 lines 1-15).

Klinger et al. teach a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide in a sample, the method comprising: contacting nucleic acid molecules in a sample with at least one primer pair of claim 7 under conditions suitable for amplification of a PKD1 polynucleotide by the primer pair, thereby generating a PKD1-specific amplification product, under said conditions; and identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample(See for example Col. 8 lines 35-60 and Col. 9 lines 47-67 and Col. 10 lines 1-40).

Klinger et al. further teach the above method of identifying the presence or absence of a mutation in the amplification product comprises determining the nucleotide sequence of the amplification product as taught in the embodiment of the assay used to detect the presence of mutation in Col. 10 for example of "direct DNA sequencing" line 35(+ Col. 8 lines 35-38).

Klinger et al. teach the method of detecting a presence or the absence of a mutation wherein a primer extension assay is used and performed with a detectably labeled primer(Col. 5 line 52) and a mixture of deoxynucleotides and dideoxynucleotides(sequencing and also see Col. 14 lines 1-10), and wherein the primer are selected so as to enable differential extension of the primer in the presence of a wild-type PKD1 polynucleotide as compared to a mutant PKD1 polynucleotide. Although the sequencing method taught by the reference(Col. 10 line 35) teaches the limitation of claim 37, the PCR reaction of Cols 13 and 14 also anticipate the limitation of 37 and 44 in their use of a sample from a subject("whole blood samples" Col. 12 line 63) to obtain their data.

Klinger teaches that the above method is performed both using a plurality of primer pairs and in a high throughput format utilizing a plurality of samples(Col. 11, lines 11-17) and further wherein identifying the presence or absence of a mutation in the amplification product is associated with the PKD1-associated disorder autosomal dominant polycystic kidney disease is also taught in Klinger(Col. 1 lines 10-49).

With regard to elected Claims 72 and 74, Klinger et al. teach SEQ ID NO:1, which includes all of the SEQ ID NOS of 3, 4, 19 and 20(See attached alignments from previous actions). While Klinger et al. define their 31,571 base pair sequence as the PKD1 genomic sequence and furthermore teach the "isolated oligonucleotides corresponding to sequences within the PKD1 gene or within the PKD1 cDNA, which alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences"(Col. 5, lines 40-55) and also "an example of an oligonucleotide that can be used in this manner(See Fig. 3B); Klinger does not teach the primer sequences of SEQ ID NOS of 3, 4, 19 and 20, only the sequences in the genomic form of their SEQ ID NO:1(see alignments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected the primers of SEQ ID NOS: 3, 4, 19 and 20 from the Klinger's known sequence of SEQ ID NO: 1 for the expected benefit of obtaining functionally equivalent primers with the ability to "selectively prevent the amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified"(Col. 5 lines 64-67)

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying

a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of PDK1, and in particular for the detection of the authentic sequence of PDK1 not homologs, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95

control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments:

Applicant's arguments filed 8/19/2005 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed in previous actions, no additional response to arguments is provided.

2. Claims 73 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991)

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 73 and 75 that includes the nesting of primer pairs one inside the other.

However, Shapira et al. teach a method of amplifying nucleic acids by way of nested primer pairs. The reference teaches that following a first round of PCR, "a second round of PCR utilizing the nested primers in Fig. 2 in a reaction mixture containing the same concentrations of all of the above constituents, except for 1.5 mM MgCl2 and a 5ul aliquot of the previous PCR reaction mixture that served as the DNA template"(Pg. 7529 left).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the nesting of primer pairs teachings of Shapira with nested the SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the

expected benefit that "nested-primer PCR provided the sensitivity to analyze…that was not available with Southern blotting techniques"(Pg. 7528 right).

Response to Arguments:

Applicant's arguments filed 8/19/2005 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were in previous actions, no additional response to arguments is provided.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
12/7/2005

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

Continuation of Disposition of Claims: Claims withdrawn from consideration are 18, 30, 58, and all claims not limited to the elected invention(i.e.1-4,6-11,16-37,39-61).